variables? It seems to me 120 milliseconds for your inclusion criteria is a pretty narrow QRS.

Related to that, was there a difference between interventricular conduction delays in people who have a true left bundle branch?

DR. LARNTZ: I can answer the first, which is that people with wider QRS had significant improvement with CRT, significant being .05. That is, wider meaning greater than, say, 160.

There was a trend toward improvement in $V_E/VCO_2$ slope. There is also the case that the adjusted improvement for the primary endpoint, actually the rate there is 37 percent reduction for that group.

You had a second question I couldn't answer.

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DR. HAIGNEY: Do you know if there was a difference left bundle branch block versus interventricular conduction delays right bundle?

DR. LARNTZ: Oh, I'm sorry. I guess I can't answer that. Not with respect to Peak $VO_2$ or others. There was one with respect to the $V_E/VCO_2$ slope, non-right bundle branch block group had greater

improvement with the device.

DR. HAIGNEY: But did you distinguish between just an interventricular conduction delay versus left bundle?

DR. BOEHMER: John Boehmer. No, that was not done. Many of these, and you are probably familiar with them, are ugly looking wide QRS complexes of the left bundle type but not meeting all criteria for left bundle branch block.

DR. HAIGNEY: Thank you.

DR. SWAIN: Dr. Krucoff.

DR. KRUCOFF: Just one quick question to check my own sense of heart failure literature. If we took patients Class III or IV heart failure who were not on ACE inhibitors and carefully initiated ACE inhibitor therapy, would it be fair to say, Mike, that we would expect if we did a $VO_2$ measurement before initiation at three months we would see an increase in their $VO_2$?

DR. HIGGINBOTHAM: Michael Higginbotham. On the average that would be true. Most of the large meta-analyses have shown a small difference .5 to 1

$VO_2$ or the exercise time equivalent to that. There might be a small change from zero to, say, three to six months.

DR. KRUCOFF: Okay. And similarly if we were to take population of Class III/IV heart failure patients and put them on a potent oral inotropic agent, would it not be true that we would probably see an increase in their $VO_2$ in about three months?

DR. HIGGINBOTHAM: Not at six.

DR. KRUCOFF: I'm not asking six.

DR. HIGGINBOTHAM: No, you're right. At three months that is absolutely right.

DR. KRUCOFF: So for a data set dominated by $VO_2$, and this is just to my point that modeling the predictive information content of a surrogate marker for clinical outcomes that are our real objective is a very important piece of understanding how in a small sort of device oriented trial environment we can or may not want to use surrogate markers or functional markers to achieve what intuitively clinically we think we are doing which is making patients better.

But we have gone down this road many times

in the history of our field in particular with stopping points along the way like three-month dominated functional evidence. We are actually in a position where we can come to the wrong conclusion.

I agree completely. I think functional measurements are not a surrogate for safety or efficacy regarding outcome data. I think I agree whole heartedly events, safety, and efficacy with regard to outcomes are completely different from functional assessments. They need to be absolutely independent. We are looking at functional efficacy and safety in this study, I think.

DR. SWAIN: Dr. Wittes.

DR. WITTES: Two quick questions. One is, I know how hard it is to classify -- I don't know -- how to classify types of hospitalization. Do you have any data on total hospitalization in the two groups? I've been involved in several heart failure studies where the total hospitalizations are actually more dramatic than those that are --

DR. BOEHMER: John Boehmer. In terms of total hospitalization, there were 115 in the CRT and

100 in the no CRT for a total of 215. Again, the data are different when looked at as time-to-first event.

DR. WITTES: So that means in large proportion the hospitalizations were not for heart failure. Isn't that surprising?

DR. BOEHMER: The hospitalizations were approximately half, 96 out of 215.

DR. HIGGINBOTHAM: It could have been that many of the hospitalizations were repeated hospitalizations in the one patient, time to initial hospitalization. Once you had a hospitalization, that was counted as not being one of those fortunate people who wasn't hospitalized which was the point of the time to hospitalization.

In fact, I understand that there were several patients that were admitted repeatedly for non-heart failure. Of course, it's incidental.

DR. WITTES: Okay. So, again, this is an issue of events versus patients.

The other issue, and I echo Warren's frustration trying to figure out what is a patient and what is an event. I calculate that there were 70

patients in -- this is the all patient group -- 70 patients in the treated group who had at least one of the events, the primary events, and 85 in the control group. Is that right?

Also, what were the numbers in the advance heart failure group?

DR. BOEHMER: Can we come back to you in a moment?

DR. WITTES: Sure.

DR. SWAIN: Okay. Dr. Aziz.

DR. AZIZ: This is a theological question that might sort of occur in the future. In patients in whom one of these devices is placed biventricular pacing and they continue to do bad, would you then switch off this biventricular pacing in that theoretical patient?

DR. BOEHMER: John Boehmer. That's a great question. We have, I believe, only one patient that has gone on to require an assist pump but we left his pacing on in that situation since we wanted great support for right heart support. The ventricular leads are tied together. We didn't see any

complication with doing that either.

DR. AZIZ: Thanks.

DR. SWAIN: Dr. Kaptchuk.

DR. KAPTCHUK: I have nothing further to ask.

DR. SWAIN: Mr. Morton, any questions?

MR. MORTON: No questions.

DR. SWAIN: Mr. Dacey?

MR. DACEY: No questions.

DR. SWAIN: Okay. I guess we'll wait here for a couple minutes. The game plan will be -- are there any other members that have questions?

Dr. Pina.

MS. PINA: Dr. Aziz's point just brought me to think that many of these centers were, in fact, transplant centers that were doing this trial. Some of these patients by $VO_2$ criteria and certainly by their six-minute walk alone would qualify for transplantation. Were these patients not candidates for transplantation? Being listed was one of your exclusion criteria, I believe.

DR. BOEHMER: John Boehmer. It was an

exclusion for anticipated within the time frame of the trial but not an absolute exclusion criteria.

MS. PINA: So do you have a number of how many of these patients were actually listed for transplant?

DR. BOEHMER: No, I do not.

MS. PINA: Were any of them on inotropes? I know there was also an exclusion for inotropes but, if they were listed, do you have any idea if they were 1Bs sitting at home?

DR. BOEHMER: John Boehmer again. I do not believe any patient was on intravenous inotropes at the time of enrollment in the study. Many patients required intravenous inotropes through the course of the study. On personal experience we did have some that went on to transplantation eventually. I don't believe any in the context of the six-month control period.

DR. SWAIN: Dr. Laskey, do you have a question?

DR. LASKEY: What happened to the poor soles who went to the lab to have the implant but for some

reason or another it was not a successful implant? Were they followed? There were 60 or 70 odd folks with the intent of implant. How did you follow them or did you?

MR. YONG: This is Patrick Yong. We followed them for 30 days after the implant to make sure there were no residual events visible from the procedure. Those patients did go on to get a standard commercially available ICD.

DR. LASKEY: Okay. But followed only to 30 days?

MR. YONG: Correct.

DR. SWAIN: Any other questions by panel members?

Do you have that answer yet for Dr. Wittes or as close as you can approximate it?

DR. BOEHMER: In terms of the total population, patients not experiencing a primary event -- I don't know if this is during the control period or total period. I think this may be total -- is 175 patients who were vent free in the CRT arm and 161 in the no-CRT. 71 percent versus 65 percent.

DR. WITTES: Those are the ones I figured out. The advance heart failure patients.

DR. SWAIN: Okay. That's fine then. What we need to do now is go through the FDA questions and ask our panel members to have comments on the questions.

The first question is to deal with safety. Are there any panel members here who think there is a safety issue either with the leads, the system, generators, or whatever?

If you want to put the questions up, that's fine. The panel members have them in front of us.

Okay, Mike.

DR. DOMANSKI: I suspect that if you go to implant these coronary sinus leads that the system is safe for what they are doing. I think that one would want to have an indication to do it, though. I think there is a risk but I don't think that risk -- I don't have any reason to believe that risk exceeds any other system where you put in coronary sinus leads. I think it's safe in the FDA sense of it.

DR. SWAIN: Okay. And were there any other

questions or does anyone else think that the adverse events or serious adverse events were a problem with these groups -- this group of patients? I think that's a no. Okay.

Does the FDA or the sponsors have any comments about the safety issues we need to address?

Okay. Next will be the effectiveness. Question No. 2. You can read up there about the effectiveness. I think we've had a great deal of discussion about the clinical relevance of the endpoints for this patient population.

The panel members would like someone to comment on 2A about the clinical relevance. We're heard a lot about statistical relevance and we've heard a fair amount about clinical relevance.

DR. KRUCOFF: I think it's a reasonable endpoint. I mean, I don't have a major problem with that.

DR. SWAIN: And the study was designed for six months and is this reasonable? Does anyone think that we should be requiring a longer than six-month follow-up?

DR. DOMANSKI: You know, I think particularly in our heart failure population that potentially unfortunately the use of the therapy in almost everyone beyond six months may make it harder to understand the benefit picture. So whether require is the right word, I actually think that longer-term follow-up would potentially be a way of better understanding the beneficial effect of the therapy if everybody didn't get the therapy.

I think there is room, though, depending on the application for using six months. I mean, if the people's exercise tolerance really was a lot better six months later, that would be a pretty useful finding so I would still wonder about long-term morbidity/mortality. I think you have to look at the individual application.

Here if the exercise had been -- you know, if all the quality of life stuff had been a lot better at six months, I think things would be different.

DR. SWAIN: I agree with you that six months in a heart failure study may well be a reasonable endpoint. Of course, if it didn't show significance,

then longer would of course be better but I think six months from my view.

Dr. Laskey, you had a comment about that?

DR. LASKEY: No. I just disagree. I think one needs to look at these events over a year, particularly when you have control groups to balance them against.

DR. SWAIN: Any other comments about the six months?

DR. AZIZ: I think a year would be a better time period.

DR. KAPTCHUK: I take it --

MR. DILLARD: Actually, one question differentiation. Jim Dillard. Could potentially those who believe that a year is a much better time point, is there any differentiation in their particular thought process about whether or not six months is adequate in order to make some sort of premarket decision versus another six months for longer-term follow-up for post-market, or are you making the differentiation that you think a year is necessary in order to judge the pre-market safety and

effectiveness?

DR. SWAIN: Dr. Laskey.

DR. LASKEY: Thanks, Jim. Well, I don't think it's fair to nail these people. I think it's a generic issue that we've not addressed. We need to address it. I think whether we need to go forth from this point on with six months more data as an additional qualification, I guess we'll get to that shortly.

I just have a personal bias that for this composite endpoint and these types of patients seeing what happens between six months and a year often surprises people. Curves diverge. They don't always track together. I just think a year is important but I don't know whether we should penalize the work in front of us for what is admittedly a subject for a lot of discussion.

DR. SWAIN: Any other comments about the year?

DR. HAIGNEY: Yes. I think I agree with that. I think the 12-month data is going to be useful for clinicians figuring out where a therapy like this

would fit in the armamentarium. I think six-month data is relevant but that shouldn't preclude doing further studies in addition.

DR. LASKEY: Yes. I mean, there's a lot of work that went into this. There's a lot of analyses that come down to not enough endpoints in a year. Well, you get your end up and, therefore, you are more likely to see something.

DR. SWAIN: Okay. 2(c) is about the subgroup that was broken out to Class III and IV. I think we have taken care of the safety issue. Is there a comment about whether these data have shown effectiveness for this device in the Class III to IV considering the statistical opinions of our FDA and panel statistical?

Dr. Domanski?

DR. DOMANSKI: No. No. I just don't think that kind of post-doc analysis is standing alone as the basis for doing anything but designing a study.

DR. SWAIN: Comments?

Dr. Aziz?

DR. AZIZ: No.

DR. SWAIN: I agree with that issue. Any others? Is there anybody who disagrees with that on this panel? Okay. No disagreement.

Question No. 3: The control group saw improvements in their functional status and quality of life, six-minute walk functional. Comment on the improvement in the control group versus the treatment group in this group. Then how does this complicate our analysis.

DR. WITTES: I think that is why you do a randomized study. I mean, I think that's what you expect and the relative comparison is prima 2.

DR. DOMANSKI: Also, there is a feeling that people in clinical trials do tend to do better. They are getting very close follow-up, for instance, in this study from people who really know what they're doing with heart failure, a very experienced clinical group. I suspect that is part of what you're saying, just good medical care.

DR. SWAIN: Hopefully the HMOs will understand the concept that actually medical care helps patients. I think that's the result.

DR. KRUCOFF: I do think there is one reality, though, that when encountering that while it is true that's why you do randomized clinical trials, encountering a lower event rate in the control population than was originally anticipated may simply mean that a study of a very important new therapy is underpowered relative to that event rate.

The potential then to take a lot of work and potentially important new therapy and ignore it is unfortunately the down side of encountering this. I would certainly think in terms of where to go from this point that understanding the influence of a lower event rate than anticipated in the control population for a therapy that, for instance, reduces the primary endpoints instance by 23 percent on an absolute basis does have at least an area of how to think about where to go from here.

DR. SWAIN: Good point.

Any other comments relating to that? Yes.

MS. PINA: I think this really highlights the difficulty with this population that can be Class III today and you diurese them, better medicate them,

and they become Class II.

The decision that you make at one point may not be the decision that you are going to make on the same patient a month later or two months later. I think that the fact that these patients were probably better medicated has a lot to do with it. I don't think it's just entering into the trial. I think it's the fact that more aggressive therapy was applied.

Which again leads me to think that I don't quite know where to fit this. That is one of my biggest concerns is how it fits with everything else that we are doing. We've made great strides in reducing mortality in this population. I wonder how much more can we do.

DR. SWAIN: I think that is a lesson learned from study design of waiting a month versus immediate turn on. The risk is higher of changes occurring.

Any other comments regarding that?

Next is comment on the clinical relevance of this control group finding has on the effectiveness of cardiac resynchronization therapy in this study. Does anyone have any further comments? It makes the data

more difficult to analyze certainly.

Mike?

DR. DOMANSKI: I think we've already discussed it.

DR. SWAIN: Beat that one to death? Okay. No. 4, whether the data in the PMA provide reasonable assurance of effectiveness for this device in the patient population study. I think you've answered that but you may want to answer that one again.

DR. DOMANSKI: I guess you can discuss it when there is a motion.

DR. SWAIN: Okay. We'll wait for a motion on that one. That seems to be the final thing.

And question No. 5 is labeling. Are there questions about labeling? We have three subquestions in this. I have one question about labeling. If we have actually showed that it certainly doesn't help Classes I and II, is it a contraindication -- should it not be a contraindication for listing Class I or II? That's the question I have.

DR. DOMANSKI: I think it's difficult to talk about. If, in fact, the hypothesis were true,

the labeling is probably reasonable. The issue is whether or not they really demonstrated that those were indications for it. I'm not sure. It's hard to see the relevance of this question frankly.

DR. SWAIN: Okay.

MR. DILLARD: Jim Dillard. I might make a comment on the contraindication. Generally FDA looks at contraindications as being supported by negative data or data which otherwise would cause some sort of adverse event that should drive a contraindication. Generally those patient populations that it would not be intended for don't necessarily need to be contraindicated. The converse of that is they are not indicated for the patient populations.

DR. SWAIN: Right. Okay. Training programs. Does anybody else have more comments on the training program? Okay. No. 7. I think No. 7 we'll talk about a little later.

The next point is that we'll ask the sponsor if they have any other additional comments or questions before we get to a discussion question.

MR. DeVRIES: No, we don't.

DR. SWAIN: Okay. Does the FDA have any additional questions or comments?

MR. DILLARD: No, not at this time. Thank you.

DR. SWAIN: Do you all have anymore? Okay.

Let's see. Now we have a discussion section which may be a little bit shorter. Usually we ask everybody to go back and other seats but there are no other seats so you can just move your microphones out and we need to have an open discussion among the panel members of any comments.

I believe, Mr. Dacey, you mentioned you were going to have another comment during the discussion section?

MR. DACEY: I always just get a little worried when I see patient information in the form of a 42-page booklet to be given to the patient. The demographics are changing so rapidly out there and the opportunities for communication are changing so rapidly. I just hope that the applicant will consider some of the options, websites, and so forth, for instructions.

Also the fact that in the demographics there are people who really can't capture this information without one on one training and somehow this be conveyed to the panel at some point that this is being done because I think the patient is often overlooked except as to what is required as far as putting the words on paper. That basically is it.

DR. SWAIN: Okay. Other further comments before the vote by panel members and before any motions?

I guess the one comments I have from doing this for a great number of years is that this is predicated on prospective studies and statistical analysis. I have actually had the experience of having patient testimonials brought in some devices and compliment the company on bringing this statistical data to be judged.

Right now we have an open public hearing part. Is there anybody in the audience that wishes to make any comments or any additional questions? Not seeing any, we'll close the open public meeting part and we'll have our Executive Secretary read the voting

options.

MS. MOYNAHAN: The medical device amendments to the federal Food, Drug, and Cosmetic Act as amended by the Safe Medical Devices Act of 1990 allows the FDA to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the agency.

The PMA must stand on its own merits and your recommendation must be supported by the safety and effectiveness data in the application or by applicable publicly available information. Safety is defined in the Act as reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions on intended use outweigh any probable risks.

Effectiveness is defined as reasonable assurance that in a significant portion of the population the use of the device for its intended use as conditions of use when labeled will provide clinically significant results.

Your recommendation options for the vote are as follows:

(1) Approval if there are no conditions attached.

(2) Approvable with conditions. The panel may recommend that the PMA be found approvable subject to specified conditions such as physician or patient education, labeling changes, or further analysis of existing data. Prior to voting all of the conditions should be discussed by the panel.

(3) Not approvable. The panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting the chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. SWAIN: All right. Do we have a motion? Dr. Domanski.

DR. DOMANSKI: Yeah. I'm going to make a motion and then support it and then hopefully let

somebody second it. I'm going to move that it not be approved. My rationale for it is this. I think, first of all, it is conceivable based on these data that resynchronization simply doesn't work.

If you assume that it does -- just assume it does. There are a lot of data out and literature. Then the question is why does the study show what it shows and I think there are two possibilities. One is that the device doesn't work.

The other possibility is that resynchronization works and the device works but the study didn't show it. I think that is quite possible. In any event, I don't think that the study as it sits provides reasonable assurance that whether resynchronization is a good technique or not, that this device actually provides clinical benefit for whatever reason. That is the rationale.

DR. SWAIN: Do we have a second for the motion on the table?

DR. KRUCOFF: Second.

DR. SWAIN: Okay. The motion has been made and seconded. Is there any discussion among the panel

members? Any further discussion before the vote?

DR. HAIGNEY: Yeah. I guess I don't agree. I think that taken in the totality of the data that is published, I think that this is most likely an effective therapy for patients with advanced heart failure.

I would think that we would change the labeling and I would want to see further study. I think that is my -- I believe that there are a couple of reasons why this study didn't come to a positive finding.

One, I think the primary endpoints are probably unrealistic. Putting defibrillators in both groups of patients you're not going to see a mortality benefit at six months. I think that the original intention of the study to look at functional variables I think is reasonable thing for this population who are generally desperately symptomatic.

I think if this study had the benefit of some of the other published studies when it was being formed, that they wouldn't have included Class II patients. I realize that the PMA as it stands did not

satisfy the primary endpoints. I guess my feeling is that there is enough data out there taken with the functional data from this that there would be enough for approval with modifications.

DR. SWAIN: Is there any further discussion of the motion that is on the table for not approval? No further discussion, then I'll call for a vote. All in favor of the motion for not approval, please raise your hands.

MS. MOYNAHAN: That's six.

DR. SWAIN: And those who are against the motion, vote no for the proposal for not approval, raise your hands.

MS. MOYNAHAN: That's two.

DR. SWAIN: Six to two. I don't vote. The motion is passed for not approval. Now I would like to ask each person to state why you voted as you voted.

DR. SWAIN: Oh, and how to bring it to an approvable point. Mike.

DR. DOMANSKI: Well, I don't actually think it would be very hard to study this in a clinical

trial. I mean, I think if I were designing this thing, I would design it from the get-go with a reasonable power and a longer follow-up if I were trying to do it.

I mean, you had an average four-month follow-up, I think. That was actually the average in the end. Wasn't it? Four and a half? That strikes me as awfully short. If I were designing a trial like this, I would be looking for perhaps a one or two-year follow-up.

I think it is very reasonable to use -- I would certainly look at mortality but I'm not sure you really even have to power it on that.

I think it is very reasonable to look at functional stuff because if you improve how they feel, and I think you could probably show that given the data that really are out in the literature, that would be reasonable rather than mortality trial. I suspect you would probably show it unless there is something that we don't understand about this device.

DR. SWAIN: Dr. Laskey.

DR. LASKEY: I think that the vendors

demonstrated safety. We don't need to belabor the efficacy endpoint. I think that perhaps the next time around go for the highest risk group, the Willie Sutton law, and use a composite endpoint such as suggested by Dr. Packer recently with a lot of creative approach to statistical modeling and statistical analysis.

I think it is fair to say, Ron, the threshold of a new era in terms of using devices for heart failure and how to choose appropriate endpoints and so forth, I think we need to give ourselves as wide a margin to look at these outcomes rather than a very narrow margin. Again, I make a strong plea to the FDA to look for longer rather than shorter intervals of analysis.

DR. SWAIN: Dr. Pina.

MS. PINA: I'll echo what the previous two individuals have said. I would really hone in on that sick population and as best possible have them on some kind of stable medical therapy for, I don't know what is the right time, two or three months.

I'm not sure if you can keep them that

stable. Hone in on that six group because my sense is that is the sick group that is going to benefit and try to find it's pigeon hole into where it fits with everything else that we're doing with this population.

DR. SWAIN: Dr. Haigney, do you have any other comments?

DR. HAIGNEY: Well, I think it's going to be a difficult study if patients have to be -- if we have to hold off on therapy for two to three months to optimize medical therapy. I think they have to get the defibrillator in once you have an indication so the design of the study has got to allow for that. You can't hold off on putting a defibrillator in if somebody has had sudden death. Anyway, I think I've expressed my --

DR. SWAIN: Okay. Dr. Krucoff.

DR. KRUCOFF: I would strongly urge this work not to start over but to continue and build on what's there including the use of the post-hoc for analysis for what is best for it. Building on hypothesize.

You now have a chronically instrumented

population in whom with a non-invasive approach you could in a randomized trial design turn this off. You have the ability to literally demonstrate Cox principles and I would strongly -- I think that would be the quickest way to really find out whether what I think you've heard across the panel is an ambivalence to say no to bring this device to market because of the intuitive sense that something good probably is happening here.

It won't come to market without the data and that is because we know like with inotropes that if you improve $VO_2$ and everything intuitively is going right at three months, there may still be more people dead than helped at the end of a year. I think you have the opportunity not to start over.

I would strongly urge you to think about taking your therapy which is in hundreds of human beings who are now well classifiable for their heart failure status and a wise statistical approach to evolving a new perspective hypothesis, rerandomize them, and turn this not clearly effective therapy off and measure functionally and quality of life endpoints

and outcome endpoints and continue and build on the work you've done so that we can get the real answer about the device and its influence on these people.

DR. SWAIN: Dr. Wittes.

DR. WITTES: It think that is a great idea. The only thing that I am uncomfortable with is I don't see evidence that it doesn't work in Class II. Before you throw away Class II I think you need to look very carefully at these data. We never saw the group that wasn't advanced III/IV. I think that you need to look at the data again and you need to do the kinds of studies that the others are talking about.

DR. SWAIN: Dr. Aziz.

DR. AZIZ: I would like to make two comments. I do hope that further data is collected. My gut feeling is there would be some benefit so I think I would hope data would be presented in the future that really strengthens the application.

DR. SWAIN: Dr. Kaptchuk.

DR. KAPTCHUK: I thought the presentation of the sponsors was really very good. I suspect personally that there's a lot of efficacy here but I

think you need a little bit more compelling data in order to put it on the market.

DR. SWAIN: Mr. Morton, do you have any further comments?

MR. MORTON: Just that I would encourage the agency to hold the requirement to a six-month follow-up. We've heard requests for longer follow-up, I think, with that cohortant patient population we are going to find lots of patients well in excess of 12 months.

And, Jim, as you suggested, perhaps look at a post-market study to get more information.

DR. SWAIN: Okay. Ms. Moynahan is going to read through how the panel members voted.

MS. MOYNAHAN: I hope I got all of these right. I was counting hands before but I think I captured this correctly.

Dr. Domanski voted not approvable. Dr. Laskey voted not approvable. Dr. Pina voted not approvable. Dr. Haigney disagreed with the main motion and I'm assuming that would mean approvable.

DR. HAIGNEY: Yes, approvable with

modifications.

MS. MOYNAHAN: With modifications. Dr. Krucoff voted not approvable. Dr. Wittes voted not approvable. Dr. Aziz, you voted approvable with conditions. Dr. Kaptchuk voted not approvable. Is that correct?

DR. SWAIN: All right. We stand adjourned. Be back at 1:30.

(Whereupon, at 12:39 p.m. off the record for lunch to reconvene at 1:30 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:33 p.m.)

DR. SWAIN: Let's get ready to reconvene. I would like to call the session this afternoon to order. This afternoon's topic is the Medtronic InSync Atrial Synchronous Biventricular Pacing Device and Attain Lead System for the treatment of congestive heart failure.

As far as the open public hearing, there were no requests to speak. Is there anyone in the audience who wishes at this time to address the topic of this afternoon's panel?

Seeing no one that wishes to speak, we'll close the open public hearing.

Executive Secretary, Ms. Moynahan, has comments.

MS. MOYNAHAN: Just to remind the speakers to introduce themselves and to state your conflict of interest.

DR. SWAIN: And for each speaker the conflict of interest is whether you are employed, own stock, or own part of a company, or you are an

investigator who is compensated for time.

We are going to start with the sponsor's presentation for the next hour or so.

DR. STANTON: Thank you. I'm Dr. Marshall Stanton. I'm the medical director for Medtronic Cardiac Rhythm Management Business. I'm an employee of Medtronic and a shareholder.

It's my pleasure to lead off the presentation of the Medtronic InSync System today. In attendance today are our principal investigator, Dr. Bill Abraham along with Dr. Anne Curtis, Dr. David Hayes, Mr. Milton Packer who will all be available for your questions.

In addition to that we have a number of people representing Medtronic who represent a cross-functional representation of people involved in the clinical trial and/or the development of the InSync System.

After my brief introduction, Dr. Abraham will present the design and methodology of the InSync study. This will be followed by Dr. Anne Curtis' presentation on the safety results. Then Dr. Bill

Abraham will conclude with the efficacy results and a conclusion.

Over a third of moderate to severe heart failure patients, those in New York Heart Association Functional Classes III or IV have ventricular dysynchrony as evidenced by QRS duration ≥ 130 milliseconds.

These patients have associated limited exercise tolerance, impaired quality of life and functional capacity and core left ventricular systolic function.

Despite important therapeutic advances with ACE inhibitors or angiotensin-II receptor blockers, beta-blockers, and spironolactone, patient well-being and exercise tolerance remain impaired.

Cardiac resynchronization therapy via atrial synchronize biventricular pacing has been proposed as a treatment for moderate to severe heart failure patients with ventricular dysynchrony.

The system under discussion today is the InSync System which is comprised of the InSync Model 8040 implantable pulse generator which has one atrial

port and two ventricular ports which supply simultaneous biventricular pacing. The device is programmed via the standard Medtronic Programmer, the 9790, utilizing the 9980 software for this device.

The leads are the Attain LV Model 2187 which is a transvenous, stylet and catheter delivered lead which is unipolar. Also the Attain CS Model 2188 which is transvenous, stylet delivered and bipolar.

Let me point out that the Attain CS Model 2188 lead is already approved and marketed in the United States for the coronary sinus application and we are seeking an expanded indication for that lead today.

Human use of the InSync System began in August of 1997 with the first implantation of the system outside of the United States. The InSync System was used as part of the MUSTIC study which began in March of 1998.

The MUSTIC study, as you may know, was a randomized crossover trial of cardiac resynchronization therapy for heart failure. These results, the MUSTIC results, were presented in May of

2000 and were published in the New England Journal in March of 2001.

The InSync study, which we will be presenting today, began in November of 1998 and was a randomized parallel study design.

With that, I will turn things over to the principal investigator for the InSync study, Dr. Bill Abraham.

DR. ABRAHAM: Thank you. Dr. Swain, panel members, ladies and gentlemen, as mentioned, my name is Bill Abraham. I am here in my capacity as overall principal investigator for this InSync study and, as such, my time has been compensated by the study sponsor, Medtronic.

I would now like to review the study design and methodology used in the InSync study. This study's purpose is summarized on this slide. The major purpose of the InSync study was to compare the effect of cardiac resynchronization therapy versus no cardiac resynchronization therapy on exercise capacity, quality of life, and functional status in patients with chronic heart failure and ventricular

dysynchrony.

In addition, the study set out to also assess the safety of CRT using the Medtronic InSync System in patients with chronic heart failure.

The study population consisted of adult patients with symptomatic heart failure who were judged to be in New York Heart Association Functional Class III or IV at baseline.

Patients were required to have a QRS duration of at least 130 milliseconds left ventricular systolic dysfunction with an LV ejection fraction of ≤ 35 percent, at least mile left ventricular dilation with an LV endiostolic dimension of at least 55 millimeters.

Very importantly, patients were required to be on a stable and optimal drug regime prior to randomization in this trial. This included an ACE inhibitor or an ACE inhibitor substitute such as an angiotensin receptor blocker if tolerated, as well as other standard therapy such as diuretics and digoxin and the requirement for these medications were a period of stability of at least one month.

In addition, if patients were prescribed a beta-blocker and, as you will see subsequently, nearly 60 percent of the InSync study patients were receiving a beta-blocker at the time of randomization, they were required to be on a stable beta-blocker regime for at least three months to minimize the confounding effects of initiating beta-blockade around the time of randomization or during the period of controlled follow-up.

This slide takes you through globally the study design for the InSync trial. Following that prespecified period of medical stability, patients underwent a baseline assessment. They then underwent an attempt at implantation of the InSync System within one week following this baseline assessment.

If the implant was successful, the patients then underwent pre-discharge randomization. This occurred within three days of successful implantation and they were randomized to either the control arm or the active therapy cardiac resynchronization therapy arm, then undergoing follow-up at one, three, and six months with six months comprising the end of study

assessment or assessment for primary endpoints of safety and efficacy.

Patients who are randomized to the control arm of this study were then allowed to crossover and, in fact, all did to active cardiac resynchronization therapy and these patients have remained in long-term follow-up with assessment every six months in an ongoing fashion.

Now, let me mention that the control group was programmed into a VDI 30 mode so that these patients had atrial tracking but inhibition of ventricular pacing. Unless the heart rate fell below 30 beats per minute, this ethically was provided as a safety net for patients who might develop a bradycardia pacing indication. The treatment arm was randomized to a VDD mode which provided atrial tracking and biventricular pacing.

In addition, I should mention that all of the analyses that you will see this afternoon are performed on an intention to treat basis. In addition, all of the p-values and all of the comparisons that are made are between group

comparisons.

In addition, and as prespecified in the protocol since the data was not normally distributed, I'll present medians and the statistical tests that were employed were non-parametric ones.

I would also like to mention to close this discussion on this slide of study design that there were some important secondary endpoints that I'll mention in some detail in a moment, but that these endpoints were assessed using core laboratories for assessment of cardiopulmonary exercise performance, echocardiography, and neurohormonal data.

Now, it is also important to note, I think, in this context the nature of the blinding of this study because one of the obvious questions regarding such a device trial is how do you adequately blind such a study.

The way that the InSync study was blinded is reviewed on this slide. Importantly, this was a double-blinded study in which the patient and the managing heart failure physician were blinded to study assignment.

Patients were given study identification cards. This identified the patient as an InSync study patient so that they could present this card to their primary physician, or if they ended up in an emergency room to minimize the risk that another physician might unblind the patient.

The heart failure staff was blinded and, in fact, this was carefully documented on a study blinding log. They were blinded to electrocardiograms, rhythm strips or any other pieces of information that might result in unblinding and this blinded heart failure staff conducted important assessments such as quality of life, six-minute hall walk, and global assessments.

There was also a blinded events classification committee that adjudicated the nature of mortality and reviewed all instances of complications or observations that occurred in this study.

Now, the way this blind could be maintained while also maintaining the high standard of patient care was to have an unblinded third party. The

unblinded third party was the electrophysiology staff. The electrophysiology staff was also listed in the study blinding log.

The electrophysiology staff served as an unblinded party which could view electrocardiograms, device implants, and other items related in particular to the electrocardiogram items which might unblind the managing physician. So in partnership the blind was maintained through a relationship between the electrophysiologist and the heart failure staff.

Finally, there was an independent safety review board that reviewed unblinded data at intervals to assure patient safety throughout the conduct of this study.

Now, this slide -- I'm sorry. The green column, at least from here, looks a little bit difficult to read. Let me take you through this carefully because this slide takes you through the study phases for the InSync trial. It is important to note the history unfolded for this study.

The initial study design for the InSync trial was that of a three-month randomized double-

blind parallel controlled study. When we initiated this study in November of 1998, we thought that a three-month period of controlled evaluation might be adequate to assess safety and efficacy.

In the spring of 1999 the FDA did signal Medtronic that a six-month period of follow-up would be preferred. Amendment 1, which went into effect in July of 1999, changed the period of controlled follow-up from three months to six months.

Then, finally after enrollment of a prespecified number of patients to meet the statistical power requirements for this study, the FDA also permitted ongoing randomization into the InSync trial in an expansion phase.

Let me expand on this a bit more. In the original three-month phrase which enrolled patients between November 1998 and June 1999, 84 patients were enrolled. Now, the reason that the figure indicates 71 is that 13 of these patients were still in blinded follow-up, were reconsented and elected to move into the six-month study.

Of 84 patients enrolled in the original

three-month study, 71 of these patients completed study after three months of controlled evaluation and 13 patients moved in to the six-month period of follow-up.

The number shown here 300 was based on a requirement to get 224 patients to six-month follow-up to meet the sample size calculation for the study. We chose 300 as a target enrollment for this pivotal phase presuming based on other device trials that the attrition rate in this study might be as high as 25 percent.

As you will see, we were, in fact, wrong and the attrition rate was substantially less representing one of the strengths of this database and so the original PMA that was submitted in March of this year is submitted based on 266 patients which was required to get at least 224 through six-month follow-up for original submission of the PMA.

As you know, in May there was an update submitted to the PMA which includes patients from this expanded phase of study. Now, with this I would like to mention that the first public presentation of the

InSync trial was made at the American College of Cardiology meeting this March.

The data presented at that meeting represented the 266 patients from the six-month pivotal phase of the InSync study and as presented publicly in Orlando at that meeting all of the primary endpoints and significant secondary endpoints were reached in that pivotal cohort.

What I'll show you today is the supplement to that PMA which also includes patients from the expanded phase.

I'm going to take you through the numbers carefully again because I don't want you to be confused about which patients we're talking about and about what happened to these patients; that is, the disposition of patients in the study.

Before we look at that, let's look at the endpoints or objectives of the trial. This slide reviews the primary safety objectives of the InSync study. They include implant success rate, freedom from device, leads, and system-related complications at six months, and a threshold or lead performance, LV

lead performance as pacing voltage threshold at six months.

Secondary safety objectives included patient survival, complication events, and observation events. The definition for complication events and observation events will be reviewed for you shortly by Dr. Ann Curtis.

The primary efficacy objectives of the InSync trial were to compare the change from baseline to six-month follow-up between the control group and the treatment group for the following three endpoints. Six-minute hall walk distance, quality of life using the Minnesota Living with Heart Failure questionnaire, and New York Heart Association classification. A prespecified distribution of ELFA is shown on the slide.

There was a requirement that all three endpoints, if met, must be met at a $p \leq 0.05$. Or any two of three endpoints could be met at a $p \leq 0.025$, or any one could be met at p-value of $\leq 0.0167$.

The secondary efficacy objectives included a variety of items that were designed to try to better

understand not only the efficacy but also potential mechanism of effective resynchronization therapy.

They included majors of metabolic exercise evaluation during standard cardiopulmonary exercise testing using a modified Naughton protocol and echocardiographic evaluation to follow cardiac changes and cardiac structure and function, assessment of changes in QRS duration, neurohormonal evaluation, assessment of health care utilization where the predominate factor considered was total base hospitalized through six months of study.

Then a clinical composite heart failure response which is an all patients randomized endpoint which has been used recently in a number of heart failure clinical trials. We'll look at the details of that composite response a little bit later.

Now let's take you through the numbers so you see how many patients were enrolled and what happened to them in this study. 579 patients were enrolled in the InSync study. Of these 43 had unsuccessful implants. Dr. Curtis will talk to you about those unsuccessful implants and tell you why

they occurred.

Thus, 536 patients underwent successful implants. Of these 536 successful implants, only four were not randomized in the study.

The reason for these patients not being randomized was that two patients developed bradycardia pacing indication between the time of implantation and randomization and, thus, the device was turned on.

Two patients developed an unstable medical condition precluding their randomization in the trial. We are left with 532 patients who were successfully implanted and ultimately randomized in this clinical trial. 269 randomized into the control arm. 263 patients randomized into the active therapy arm of this study.

Now, this is a relatively busy slide so let me spend a few minutes here and take you through it because I think one of the strengths of this database is that there are really few study exits and the data set is fairly complete. You need to understand what the numbers are here so we now follow on from the previous slide. 269 patients randomized to the

control group and 263 patients randomized to active cardiac resynchronization therapy.

Let's start with the control patients. Of these 269, 43 patients were randomized in the original or initial three-month phase of this study. Of these five consented to be followed in the six-month amended protocol so that 226 patients were randomized into the six-month protocol.

An additional five patients from the initial three-month protocol consented to be followed in the six-month protocol which yields a total of 231 control patients who comprise the six-month data set.

Similarly, in the resynchronization group there were 263 patients who were randomized. 41 were randomized into the initial three-month phase of the study. Of these eight patients agreed to be followed in the six-month protocol combined with the 222 patients randomized into the six-month protocol, there were 230 active resynchronization patients available for the six-month data set.

Now, let's look what happened to those patients and we'll look ultimately at the number of

patients that will be available for evaluation of efficacy in this trial. As I'll reiterate in a few moments, all of these patients were used for assessment of safety.

Now, the first group that is not included in the analysis shown today are patients who at the time of closing, locking, and cleaning this data set for preparation of the PMA and supplement were still in double-blind following.

These are not patients that have been lost to follow-up. There are not missing data points. These are data points that were not available at the time of closure of the database for presentation at this meeting. 26 patients exited the study due to mortality, 16 in the control group and 10 in the resynchronization group.

One patient in the control group underwent a heart transplant. Two patients, one in each group, exited the study due to explanation of the device which was related to infection. Finally, there were nine patients who were not available for assessment during their six-month window.

This leaves assessable for efficacy 171 patients in the control group and 174 patients in the resynchronization group. This will be the group of patients that we will focus on in our discussion of efficacy. Again, the discussion of safety will include all patients.

Finally, I should mention that the number of patients available among those assessable for efficacy was quite high. Follow the Ns as we go through the slide and you'll see that they are either identical to or very closely approximate the numbers shown on this slide.

Let's take a look at patient demographics. I am going to review with you patient demographics for this cohort of patients analyzed for efficacy. You should know that if one looks at the entire cohort, the numbers are identical.

Starting at the top, you'll see that this is a fairly typical group of patients with moderate to severe heart failure. On average they are about 65 years old. 31 percent of the InSync trial patients are women. 90 percent are caucasian. About 91

percent had Class III heart failure baseline. About nine percent at Class IV.

The average cure restoration at baseline was 165 milliseconds. You'll see that the ventricular function was quite poor. The average LV injection fraction averaged 22 percent. The average LV endodiastolic dimension about 69 millimeters.

Some additional patient demographic information is presented on this slide. You'll see that the etiology of heart failure was about evenly split between ischemic and non-ischemic etiologies of the disease.

At baseline the six-minute hall walk distance averaged around 300 meters which is compatible with a predominately Class III population of patients. Data is presented on the slide for baseline heart rate and blood pressure, but I would like to focus your attention on the bottom three rows of the slide which look at drug therapy confirming that the study met its intended goal of having patients treated with optimal background medicines at the time of randomization.

94 percent of patients were receiving a diuretic. 93 percent of patients were receiving an ACE inhibitor or angiotensin receptor blocker. Nearly 60 percent of these patients were on a stable beta-blocker regime at the time of randomization in the trial.

The next slide looks at stability of heart failure medications in this trial. While certainly treatment of the patient and the patient's heart failure came first, we did ask investigators to try to maintain drugs as constant as possible throughout the six-month period of study.

What you will see here is that in both the control group shown in white, as well as the resynchronization group shown in yellow, that the percent of patients who are either on or off these medications at baseline changed very little during the conduct of this study. In fact, more than 95 percent of patients in both groups demonstrated stability of this background medical regimen.

I would like to just summarize the methodology for the InSync trial. As you have just

seen, heart failure medication stability was maintained. Changes were not common and were balanced between the groups.

In terms of safety data, the presentation of primary safety data that will follow by Dr. Curtis includes all implanted patients. That is that N of 536. The comparative results for safety; that is, the comparison between the control and the CRT arms by definition includes all randomized patients and recalled that the N here is 532.

In regard to efficacy data, comparative results includes all randomized patients that had completed six-month follow-up at the time that this PMA submission was prepared. Please recall that the analysis is performed on an intention to treat basis.

With that I would now like to introduce Dr. Anne Curtis from the University of Florida who will review the primary safety results of the InSync trial.

DR. CURTIS: Thank you. Dr. Swain, members of the panel, my name is Anne Curtis. I am a cardiac electrophysiologist at the University of Florida. I was a site principal investigator for the InSync

system and a member of the clinical events committee.

I do speaking engagements for Medtronic and my time and expenses for attending this meeting are being reimbursed. My job now will be to present the primary safety results for the InSync study.

As Dr. Abraham mentioned previously, the key components of safety for the trial were, No. 1, implant success. Secondly, freedom from complications related to either the generator, the lead system, or the system in total, as well as pacing voltage threshold out at six months.

I want to review definitions that were used throughout the study as to complication and observation. The definition used in the panel pack for a complication was an adverse event that is resolved invasively or which results in the death of or serious injury to the patient or in the termination of a significant device function. I would like to add this also includes the use of intravenous medications of any kind.

An observation is an adverse event that is resolved by non-invasive means or resolved

spontaneously. A system related complication is a device related complication that occurs after the initially implanted functioning system comprised of the Model 8040 InSync generator, a Model 2187 or 2188 lead, as well as the right atrial and right ventricular leads.

I would like to add that these definitions of complications and observations are fairly standard and have been used in previous device trials.

This diagram here shows where the leads wind up being placed schematically. What you have here is a right atrial lead. There is a right ventricular lead. Then in yellow is the left ventricular lead coming in through the coronary sinus and into a branch. You can see that branches of the coronary science are labeled here. Lateral, postero-lateral, anterior great cardiac vein, posterior cardiac vein, and middle cardiac vein.

The number of branches, the size, and how many options you have for placing a lead in an individual patient is entirely dependent on their anatomy. It would be very unusual to have a patient

who had all these options at once.

Generally speaking you have two or three places that you know that you can aim to put the lead in. The goal of implantation in general was to try to get a lateral position to try to get separation as much as possible between the left ventricular and right ventricular leads.

What you are going to see now is a video of the implant process. What will be coming up first, this is the guide catheter, two different curves that was available that accesses the coronary sinus.

Here is the guide catheter being placed into an introducer. From there the guide catheter is placed in the right atria and then into the coronary sinus.

Here through the guide catheter is placed a balloon tip catheter. The balloon is inflated and then contrast is injected to illuminate the branches of the coronary sinus. From there we pick our targets.

What you will see next is the lead itself. The lead with the stylet pulled back has a curve on

the end of it. As you advance the stylet it straightens out the tip. By pulling the stylet back and advancing it, you can change the curve on the end to help you get into the branch of the coronary sinus.

Here is the lead being placed through the guide catheter, the stylet being advanced, and then the lead as it's placed into the coronary sinus and then a branch. This is in the approximate location of one of the branches of the coronary science.

Then finally another view showing all three leads in place in the patient.

This is the InSync generator. It has three ports to it. The bottom two ports are for placing the left ventricular and right ventricular leads. The top port is for placement of the right atrial lead.

Now I'll review the primary safety objectives. The first one was implant success result. The predetermined performance objective was that we would have at least 80 percent successful implants. The observed rate in the trial was 536 successes out of 579 attempts. The overall success rate was 93 percent.

The lower limit of a two-sided 95 percent confidence interval was 90 percent and so the implant success objective was met in the trial.

I review here the reasons for unsuccessful implants. The major reasons included inability to access a coronary vein or to obtain a distal location or dislodgement or an unstable location of the left ventricular lead. Other reasons included elevated pacing threshold, cardiac vessels being too small, or phrenic nerve stimulation.

These really are the primary reasons that we run into trouble. Some patients it's difficult to access the coronary sinus with the guide catheter. Sometimes you get in there and you can't get the lead manipulated out. In the overwhelming majority of patients, it is possible to get a stable location that will stay as we showed.

Here we review the implant dissection and perforation events. I want to call your attention first to the column on observations. Remember that I said that observations are something that you see, that you observe, but that requires no invasive

intervention. There were 19 instances of coronary sinus dissections and 10 cardiac vein or CS perforations.

What we mean by this in general there would be a blush. You put some contrast in and it stains. You see it on fluoroscopy but there is no change in hemodynamic status of the patient. You note it, you write it down on the event forms but nothing had to be done.

Now let me go through the complications here. These are patients who did require more intervention. There were four instances of coronary sinus dissections and two cardiac vein or coronary sinus perforations for a total of six in the trial.

These were resolved in the following ways. One patient had the procedure aborted at that point and came back several days later and had successful implantation of the entire system.

Another patient had a trans-esophageal echocardiogram performed and because that's an invasive procedure, it was counted as a complication even though nothing was done on the basis of that.

One patient had a central line placed and three other patients received some kind of intravenous medication such as dopamine for some period of time. No patient required pericardiocentesis. There was no operation necessary. No deaths related to this.

Now I'm going to review the freedom from InSync Model 8040 generator device related complications. There was only one complication in this category. One device had to be replaced in a patient due to inappropriate sensing function. The observed rate at six months was 99.8 percent.

The performance objective was at least 90 percent freedom from complication and the lower limit of a two-sided 95 percent confidence interval was 98.4 percent. This performance objective was met.

Now we will look at the freedom from Attain Model 2187 and 2188 LV lead related complications. There were 48 events in 38 patients for an observed six-month rate of 92.5 percent.

The performance objective was at least a 75 percent freedom from lead related complications. The lower limit of a two-sided 95 percent confidence

interval was 89.8 percent. This safety objective was met in the trial.

This slide shows what kinds of complications were seen. Out of the 536 implants there were 48 events in 38 patients. You see the N shows the number of complications and on the right the number of patients. Many times a patient who had a lead dislodged would have an elevated threshold determined and both of those might be detected in one patient.

These are some instances where leads did move, thresholds became too high, patients did need to be reoperated on to reposition the lead.

This shows what the outcome was, the resolution of these complications. In 25 patients the leads were repositioned. In nine patients the leads were replaced. One patient had an invasive evaluation to confirm capture but nothing needed to be done about it. There was adequate capture.

There was one instance where there was inability to capture but no repositioning attempt was made at the patient's request. Then there was a lead that was explanted because of a failed repositioning

attempt. Then finally there was one patient who had hypotension and required IV fluids when the lead was being repositioned.

The safety objective No. 4 was InSync system related complications and freedom from that problem. The performance objective was that there would be at least a 70 percent freedom from complications related to the entire system, all three leads and generator.

There were 74 events and 55 patients. The observed rate at six months was 89 percent and the lower limit of a two-sided 95 percent confidence interval was 85.9 percent. This safety objective was met as well.

This slide shows the performance objective at the 70 percent level and what the actual outcome was from the trial showing that the safety objective was met. Out of the events that were seen there were 74 total and 55 patients. The breakdown is shown on this slide.

I've mentioned previously that one was related to the InSync generator itself. There were 48 events in the patients related to the Attain LV leads.

There were 10 instances where the right atrial lead dislodged and needed to be replaced. There was some problem with it.

Five instances where the right ventricular lead was a problem. There were nine cases where the system was explanted. Seven of them were due to infection. In two instances patients developed an indication from an ICD. The system was replaced with an ICD. There was one instance where there was a problem with the right atrial and right ventricular lead both in one patient.

Finally, the last safety objective was the lead pacing threshold performance. The performance objective was that at six months that the threshold would be no higher than three volts. The results from the trial show that the mean six-month pacing voltage at six months was 2.22 volts.

The upper limit of the two-sided 95 percent confidence interval was 2.36 volts. This performance objective was met shown on this slide by the fact that at six months the threshold was lower than the predetermined performance objective.

In summary the primary safety results from the InSync trial show that all primary six-month safety objectives were met including implant success and six-month device related complications attributed to the generator, the leads, or the system in toto. As well as the fact that the six-month pacing threshold performance was met.

The last thing I just want to cover briefly since we're talking about implantation right here is just briefly about the objectives of the training program for the system.

What would be critical for any physician who was going to be implanting a system is that he or she should be able to achieve success at implantation of the cardiac resynchronization system.

That would include the assembly and use of the LV lead implant tools, the ability to successfully implant the LV lead, as well as to understand device operation, to ensure therapy delivery including the determination of biventricular pacing thresholds.

The components of such training would include use of a heart model that allows one to

practice lead placement prior to the first implant. The use of an implant video which would provide an overview of the system implant including case examples.

One-on-one training which would cover the concepts of resynchronization, biventricular threshold management, and follow-up as well as review of case studies.

What I would like to do now is turn the podium back over to Dr. Abraham who will discuss the efficacy results from the trial.

DR. ABRAHAM: Thank you. Next slide. Let me remind you that the primary efficacy objectives of the InSync study were to compare change from baseline to six months follow-up between the control and treatment groups for six-minute hall walk, quality of life score, and New York Heart Association class. We will now in turn take a look at each of these objectives.

This slide shows the change in distance walked in six minutes in patients randomized to the control versus CRT groups. The left-hand panel of the

slide, and you'll see that some subsequent slides are set up in a similar fashion, shows the data over time at baseline 1, 3, and 6 months evaluation. On the right-hand panel of the slide you will see the median values, plus the intercortile ranges as well as the applicable p-value.

What you will see here is that there was little placebo effect seen in the control group. There was at most a modest improvement in six-minute hall walk distance seen in patients randomized to the control arm. The change in median value in the control group was about 9.8 meters.

In comparison, there was a marked improvement. The difference in medians is 40 meters seen in the resynchronization group, and the p-value here was highly significant at the .003 level.

Similarly on the next slide you will see the cardiac resynchronization therapy also produced a highly significant beneficial effect on quality of life.

Now, in contrast to the prior slide on six-minute hall walk you will see that there was a

substantial placebo effect seen in terms of quality of life. In the control group there was a nine point improvement in the Minnesota Living with Heart Failure questionnaire score. Despite this marked placebo improvement, there was a treatment effect which exceeded the placebo effect. The median change in the resynchronization group was 18.5 points. Again, the between group difference is highly statistically significant.

Finally, of the three primary objectives, this and the next slide present effects of resynchronization therapy on New York Heart Association functional class ranking. This slide presents the data looking at patients who either improved New York Heart Association class by at least one class, patients who were unchanged at six months, and patients who worsened New York Heart Association class by at least one class at six months.

You will see here that when one looks at the distribution of New York Heart Association class changeover six months that there is a highly favorable affect of cardiac resynchronization therapy with a p-

value of less than .001.

For example, 68 percent of resynchronization patients improved by at least one class compared to only 38 percent of patients in the control group. While the percentages are very small, fewer patients demonstrated worsening New York Heart Association class in a resynchronization arm.

The data is presented a little bit differently on this slide. It shows the change in distribution of New York Heart Association class from baseline to six months.

In control patients shown on the left-hand side of the figure and resynchronization patients shown on the right, again you'll see that there was a highly favorable effect of resynchronization therapy on New York Heart Association class with, for example, 63 percent of resynchronization patients improving the Class I or II heart failure compared to only 33 percent in the control arm of study.

This slide looks at the proportion of patients with any two or all three of the following levels of improvement. An improvement of New York

Heart Association class of at least one class and improvement of quality of life of at least 13 points, and/or an improvement in the six-minute hall walk distance of at least 50 meters.

These numbers were chosen because they are the ones that were used for sample size calculation in this study. You will see that in all instances whether one looks at any combination of two of these three endpoints or all three resynchronization therapy produced a highly favorable impact on these objectives as measured.

So in summarizing the primary efficacy results of the InSync study, each of the primary efficacy objectives was met with significant improvements in six-minute hall walk, quality of life, and New York Heart Association functional class ranking.

Now let's take a look at some of the secondary efficacy results from the InSync study. The first shown are results from the cardiopulmonary exercise core laboratory. The reason that the ends here are smaller than ends reported on previous slides

is that not all data has been analyzed by the core laboratory. Every cardiopulmonary exercise test, and there were a substantial number of them, are being reviewed at a single core laboratory at the University of Cincinnati.

The left-hand panel of the slide shows effects on peak oxygen consumption. The right-hand side total exercise time. You'll see that the message is similar in both figures. There was little, if any, improvement seen in patients randomized to the control arm of this study.

For example, the median change in the control group for Peak $VO_2$ was just 0.1 ml per kilogram per minute. In comparison the median change in Peak $VO_2$ in patients randomized through resynchronization therapy was 1.0 ml per kilogram per minute and its between group difference was significant.

Similarly, resynchronization therapy produced a significant improvement in total exercise duration. The difference here is 85 seconds.

This and the next slide shows some data from

the echocardiographic core laboratory. For time sake I will not show you all of the data available from this core laboratory, but it all looks the same and the message here is that resynchronization consistently improved all measures of cardiac structure and function.

This slide shows effects of resynchronization therapy on left ventricular ejection fraction and mitral regurgitation. Again, common theme here. Little effect seen in patients randomized to the control arm. In contrast there was a marked improvement.

The difference here a little bit more than five LV ejection fraction units favoring improvement with resynchronization therapy. You'll see that there was also a highly significant reduction in mitral regurgitant jet area seen in the patient's randomized through resynchronization therapy.

Similarly on the next slide is data on left ventricular endodiastolic dimension and left ventricular mass. In regard to LV dimension you will see that the control group demonstrated no change in

LV endodiastolic dimension. In comparison there was a .4 centimeter or 40 ml reduction in LV endodiastolic dimension. This was paralleled by an improvement in LV and systolic dimension as well.

Interestingly, while the control patients demonstrated a progressive increase in left ventricular mass over six months, patients randomized to resynchronization therapy actually experienced a decrease in LV mass and the between group difference was significant at the p.006 level.

This slide looks at the change of resynchronization therapy on cure restoration. You'll see as expected there was no median change seen in patients randomized to the control group. There was a median difference of 20 milliseconds seen in those patients randomized to active therapy.

In regard to neurohormones there was a neurohormone core laboratory in John Burnette's laboratory at the Mayo Clinic. The neurohormones listed on this slide for evaluated prospectively and serially in this study.

While the data is incomplete, to date no

statistically significant difference in change from baseline to six months between the control and CRT groups has been shown for any of these neurohormonal parameters.

Now let's look at our primary measurement of health care resource utilization. I do want to move through the presentation quickly to keep us on time, but I am going to spend a moment here to make sure that you understand the data that is presented on this slide because it is presented a little bit differently than what's in the panel pack. It's the same data but it's presented a little bit differently.

In the panel pack what is presented is a comparison between number of hospitalizations and length of stay. But from the standpoint of health care resource utilization, the most important driver of health care resource utilization or cost here is total days hospitalized and we analyze this through six months through the double-blind controlled period of study.

That's what is shown on the slide. It is shown for all-cause hospital days on the left-hand

panel of the slide and for hospital days attributable to heart failure shown on the right-hand panel of the slide.

Let's start on the left-hand panel of the slide where you will see that in the control harm 60 patients were hospitalized 99 times for a total of 664 all-cause hospital days.

In comparison in the resynchronization group, 57 patients were hospitalized 80 times for a total of 275 all-cause hospital days. This represents a 59 percent reduction but this did not reach a level of statistical significance which when referenced to the entire cohort of patients randomized in this trial.

On the right-hand panel of the slide you will see that in terms of heart failure hospitalization where we might expect the therapy to have its greatest impact, in the control group there were 27 patients hospitalized a total of 39 times for 302 heart failure hospital days.

In the resynchronization group there were 14 patients hospitalized 20 times for a total of just 56

heart failure hospital days. This represents an 81 percent reduction and is associated with a p-value of less than .05.

Now I would like to turn to the composite clinical response. I know that many of you are familiar with this composite response which has emerged as one of the most useful endpoints in contemporary heart failure clinical trials. Because of that, we made this one of the secondary endpoints of the InSync study.

According to this composite clinical heart failure response, patients can be categorized into one of three groups based on the definition shown on this slide. Patients are judged to be improved if they have an improvement in either the New York Heart Association class or patient assessed global status.

They are judged to be worsened if during the six-month period of double-blind study they died, they developed worsening health failure leading to hospitalization or permanent withdrawal therapy, or if they had either worsening of New York Heart Association class or global assessment. Finally, if

they don't fit either of these definitions, they are judged to be unchanged.

The next slide presents the results for this composite clinical heart failure response. You will see that it highly favors an improved outcome with resynchronization therapy.

Moving from left to right you will see that more patients in the resynchronization group improved 65 percent versus only 39 percent in the control group and fewer patients worsened and the p-value here is highly significant at the $p < 0.001$ level.

Now I would like to look briefly at some of the secondary safety results. The reason for presenting them in this part of this presentation is that many of these relate to heart failure outcomes. Let's take a look at these.

First is to characterize patients survival. You will see here that looking at the whole cohort of patients followed to date, there have been 19 deaths in the control, 14 deaths in the resynchronization group for a total of 33 deaths in this population.

This turns out to an estimated six-month

survival in the control group of about 92 percent and in the resynchronization group of about 94 percent.

These are statistically indistinguishable but it is about six to eight percent six-month mortality rate which is compatible with what we would expect from a predominately Class III heart failure population.

The next slide looks at the causes of death. Again, there were 19 deaths in the control group and 14 in the resynchronization group and there are no statistically significant differences between either total mortality or cause-specific mortality in this study.

This slide presents the Kaplan-Meier analysis of this data. You will see here that there was, as mentioned, no statistically significant difference. The relative risk here is .74 favoring resynchronization therapy, but I don't want to overstate it. Really what this slide shows is that there is no difference in all-cause mortality in the resynchronization patients or those randomized to control.

Let's look at some of the complications and observation events during the randomization period in the trial. I'm going to tell you why I'm taking you through these numbers a bit carefully because one of the questions that has been raised has been in regard to the total number of events in this trial.

First of all, we asked investigators to report any event, complication or observation that might have occurred. You should know that the majority of such events, in fact, were not device or therapy related and may have included such items or such complaints as headache or insomnia.

In addition, it should be noted that, as one would guess, a major contribution to these events is seen in typical heart failure type events such as heart failure decompensation or arrhythmias. Yes, when we start off with the total number of events, there are more than 800. But realize that the number of patients affected is substantially smaller than the number of events.

Also appreciate that the event reporting on this slide, the categories are not mutually exclusive

so patients had multiple events in multiple categories. The bottom line is you have already seen presented by Dr. Curtis that the number of events, either complications or observations attributable to the system or to the procedure, were relatively few and, in fact, comprise a minority of the overall reporting of adverse events in this study.

I would also like to focus a bit on the heart failure events which might provide us some additional insight into this therapy.

This slide looks at overall heart failure decompensation events stratified as complications and as observations and then substratefied based on the way they were categorized by the events committee.

Complications required either IV diuretic of the decompensation and IV inotrope for treatment of the decompensation, or other intravenous or invasive means of therapy and observations which might have included treatment with an increase in the oral dose of the diuretic or an increase in the ACE inhibitor or diuretic dose or some other change in treatment.

Or, in some instances, patients had a

documented episode of worsening heart failure without a clear treatment change.

You'll see that when one looks at this data, it appears -- again, I want to be very cautious here. I do not want you to think that I'm trying to overstate the data -- but it would appear that there are fewer such heart failure decompensation events in the patients who are randomized to resynchronization.

For example, the totals are 151 versus 85, complication 65 versus 26. Look, for example, at the use if IV inotropes. 19 episodes of decompensation in control patients were treated with an IV inotrope compared to only one such instance in the resynchronization group. This data is inherently weak and this is a post-hoc view of the data.

Let's take a look at some additional endpoints which may give us further insight into the effects of the therapy.

Extending those observations of worsening heart failure events now to a Kaplan-Meier analysis, this slide shows the combined endpoint of death or worsening heart failure requiring hospitalization.

Again, appreciate that this is a post-hoc analysis and the p-value is nominal. But you will see here that there was a risk reduction of 39.5 percent and the p-value is .056 favoring resynchronization therapy.

To extend this observation based on the data shown on the previous slide and including all serious instances of heart failure decompensation. Now those that require hospitalization or treatment with intravenous medications, you'll see that the relative risk reduction is even better, about 42 percent, and the p-value has gotten smaller as more events have been added into this analysis.

Let me try to bring this all together with a clinical summary and some clinical perspective. Cardiac resynchronization therapy based on these observations is effective in New York Heart Association Class III and Class IV heart failure patients.

The InSync study used standard heart failure endpoints such as quality of life, New York Heart Association class, and the six-minute hall walk.

The InSync study demonstrated remarkable consistency across all endpoints. There were no instances in which the control group did better than the active therapy group. In fact, there were no instances in which the control group did as well as the resynchronization group. So the concordance or consistency of effect here is really quite striking.

Remember that the improvements were seen on top of standard heart failure medical therapy on top of ACE inhibitors, diuretics and, in large part, beta-blockers. The positive results were seen despite the presence of an expected placebo effect.

Finally, the magnitude of effect compares well with other proven therapies such as ACE inhibitors, beta-blockers, or Digoxin.

Let me just show you some examples of that on the next two slides. This slide compares cardiac resynchronization therapy using the outcomes from the InSync trial to our experience from a variety of trials with ACE inhibition and beta-blockade.

Again, for time sake, I will not take you through this in a detailed fashion. I'll let you scan

the slide on your own. The two important messages here are that, one, like the ACE inhibitor and beta-blocker trials there is a placebo effect and that is not unexpected.

Despite that placebo effect, there is highly significant treatment effect and the magnitude of effect is at least as good, at least comparable, to that seen in the ACE inhibitor and beta-blocker trials.

Someone earlier very astutely mentioned that these ACE inhibitors and beta blocker trials didn't always show such great improvement in symptoms or quality of life but they affected other endpoints like survival.

Let's look on the next slide at another drug which we know has a neutral effect on survival but improves patient symptoms and functional capacity and that is Digoxin.

You will see that the comparison looks similar to that shown on the previous slide that the magnitude of effects seen with resynchronization therapy is at least as good that the control

improvement is similar in these sorts of trials, specifically referencing the RADIANCE study so resynchronization fairs well in the setting of standard heart failure therapy.

While I'll conclude with this slide, the New York Heart Association Class III and Class IV systolic heart failure patients with intraventricular conduction delays. Cardiac resynchronization therapy is safe and well tolerated.

It improves quality of life, functional class, and exercise capacity. It improves cardiac function, and it importantly improves heart failure composite clinical response, an integrated measure of heart failure outcome.

With that, I will conclude my formal comments and we would be happy to address your questions at this time. Thank you.

DR. SWAIN: Thank you. We'll hold on the questions. Next we'll have the FDA presentation, Dr. Mitch Shein.

MR. SHEIN: Good afternoon. As Dr. Swain mentioned, I'm Mitchell Shein. I'm the lead reviewer

for P010015, the Medtronic InSync Cardiac Resynchronization System.

The PMA has been reviewed by a number of people within the Division of Cardiology as well as outside from other offices in the center. They include Frank Lacy who looked at the preclinical testing for the 8040 device; James Cheng who reviewed the software; John Glass from the Office of Compliance who looked at the manufacturing and sterilization sections; Vertleen Covington who did the data integrity from our bioresearch monitoring staff; and Dr. Barold and Dr. Gray, who you've heard from today, who will also be reporting here to talk about the clinical and statistical review.

The regulatory history behind this PMA obviously started as a dimension under IDE under G980219 back in 1998. Medtronic elected to submit a PMA modular shell under the number listed there. Modular shell is a system that we have within the agency for reviewing elements not including the clinical data ahead of the time of the submission of the PMA.

The modular shell for this particular device included the six listed. They included the preclinical testing for the post generator, the software verification validation, animal testing for the leads, animal testing for the InSync system as a whole, as well as the manufacturing and sterilization modules.

The InSync components that we're talking about today in this system includes the 8040 generator, the 9980 programmer software for use on the 9970 programmer, and the Attain models 2187 and 2188 leads.

Before we get into the meat of today's discussion which will include the clinical data as well as the statistical information, I wanted to backtrack a little bit and talk about all the testing that is going on before that.

This is a slide including the highlights of the model 8040, the post-generator preclinical hardware testing including IC/Hybrid testing. Those system components are identical to Thera-i. The battery was used in the Kappa 400 contains IS-1

connectors and, therefore, had the testing commence with that standard.

It underwent significant environmental and mechanical testing. It was subjected to electromagnetic compatibility testing. Biocompatibility testing was waived due to the identicality to Kappa 400 parts.

Now, in the panel it was mentioned there are outstanding issues regarding this. Those issues are minor and have since been resolved. This module is now closed.

The 9980E software. The information was submitted, Medtronic typical software development plan included the software application specification. It provided us with a detailed software development plan itself, hazard analysis, and extensive verification testing. This module two has been closed out and we have no further issues there.

The Attain model 2187 and 2188 leads, as Dr. Stanton said earlier, the 2188 is currently approved. They are looking for an expansion and indication for the use of the system at this time.

The testing that these devices underwent for this study included environmental conditioning, mechanical, electrical testing. Again, the biocompatibility testing by virtue of the identicality of the materials and commercially available products has been included. Of course, sterilization qualification information.

I now want to turn the floor over to Dr. Barold who is going to go and review the clinical.

DR. BAROLD: Good afternoon. I'm going to take this chance to go over the clinical summary for Medtronic InSync Cardiac Resynchronization System. In my presentation I will also include the statistical analysis performed by Dr. Gerry Gray.

I would just like to remind you of the indications for use statement as given to us by the sponsor. It is for patients with advanced heart failure who are New York Heart Association Class III or IV and have a left ventricular injection fraction of $\leq$ 35 percent and a QRS duration of $\geq$ 130 msec.

I just want to briefly remind you again of the study methods. All patients received an implant.

Three days after the implantation they were randomized to either pacing on or pacing off for six months at which time the investigators were allowed to turn the packing on. As you heard from the sponsor, all of the investigators chose to turn the pacing on.

There were three co-primary effectiveness endpoints studies. New York Heart Association classification, quality of life score as measured by the Minnesota Living with Heart Failure questionnaire, and the six-minute hall walk distance, and the appropriate statistical testing done which was explained by the sponsor.

The primary safety objectives were also gone through by the sponsor. As were the secondary safety objectives which are listed here. And the secondary effectiveness objectives.

I just want to remind you of some of the inclusion criteria. Patients were required to be a New York Heart Association Class III or IV at the time of enrollment. They had to have a QRS > 130 msec.

They were required to have a stable medical regimen for one month excluding beta-blockers which

had to be on a stable beta-blocker regimen for three months prior to enrollment. They additionally had to be on a stable dose of positive inotropic OP Rx for one month prior to enrollment.

I just listed the exclusion criteria. The only one I really want to point out is the patients who were not allowed to have an actual indication for a pacemaker in this case. Otherwise they are standard criteria for these types of studies.

Patient accountability. As you heard, there were 631 patients enrolled. We will be looking at the six-month paired data for 171 controls and 174 treatment patients.

Here are the baseline characteristics for all of the patients that were enrolled. Again, as the sponsor pointed out, a large percentage of these patients were on ACE inhibitors and beta-blockers. I would also like to point out that the ischemic etiology is approximately 50 percent or so in this patient population.

I'm going to move on to the actual results. Again, these are paired results and I will be talking

mostly about the six-month results but will be mentioning some other three-month results.

Most of the data presentation will be in this same type of format. You can see the median result for the control and the treatment and then the difference of the median results there. As you can see, there are only four categories in the New York Heart Association class.

Therefore, the median control class did not really change across three to six months. Whereas the median control class of treatment decreased from three to two which was statistically significant.

This slide gives you some information on how many patients actually improved by one or two New York Heart Association classes or had a worsening of their condition. As you can see, in the control group 38 percent of patients had an improvement in their New York Heart Association classification, whereas 68 percent of the patients in the treatment group had an improvement.

I think interesting also is that there was only a four percent worsening in the control group and

a two percent worsening in the treatment group.

This is a quality of life results. Again, it's paired, median results. You can see at the six-month point that the control group had a nine percent difference, a negative score. The more negative it is, the better it is for the patient. They had -9 versus -18.5 with a p-value of 0.003 at the six-month point.

This is a slide a statistician put together from the actual data. You can see a tremendous amount of variability. Again, the data with the colored lines representing the median values. That just gives you a nice spread of scores.

Just to summarize the quality of life results at the six-month point, you can see in the control group 67 percent of the patients improved in their quality of life scores and 79 percent of the patients with treatment improved.

This is similar data again presented for the six-minute hall walk distance. You have seen this from the sponsor. In the control group at the six-month point you can see the numbers here, an

improvement of 9.8 and then in the treatment group an improvement of 40.1 meters with a p-value of 0.003.

Again, this is a slide put together by a statistician which shows the actual individual result and showed the results there for the control and the treatment group.

Out of the control group 56 percent of the patients had an improvement in their six-minute hall walk as opposed to 69 percent of patients in the treatment group.

Overall results, which the sponsor has gone over, quality of life score, there was 9 unit difference in improvement over the control. IN the hall walk there was a 30 minute difference, a 30 meter improvement in the treatment group versus a 10 in the control, and a 1 class difference in improvement over a 0 class difference in the control group in the New York Heart Association classification.

The sponsor presented a graphical representation of the slide. The information here is just to show you what percentage of patients in the control and treatment group improved at either one of

the individual endpoints or the combination thereof.

These are some of the secondary endpoints, QRS duration. I would just like to note that the way that this was measured was in the control patients they took the echocardiogram and then in the treatment patients they did measure the QRS during pacing. You can see that there is a difference in the QRS duration between treatment and control.

This is the data from the Peak $VO_2$ at the six-month point. You can see that there is more of an improvement in the treatment group with a p-value of 0.038.

Just wanted to show you the 12-month data for the treatment group only. The reason that only the treatment group is on here is because, as you know, at the six-month point in the control group, they are actually then considered treatment groups just for ease of information.

You can see the median paired numbers at baseline and three months, at baseline and six months. Then at the 12-month data you can see baseline and 12 months. I also want you to just note that there are

only 59 patients in that 12-month data.

Exercise time in seconds. Again, there was a larger improvement in the treatment group.

This is a list of the echocardiographic parameters with the exact amounts of improvement in the control and treatment group. These numbers have been available to you so I won't go through each one of them. You can see some of the amounts of increase or decrease in these particular variables.

This is the health care utilization that the sponsor spoke about when they discussed the number of hospitalizations. You can see here in the control group that there were 16 hospitalizations, in the treatment group 57 hospitalizations. Of those 27 hospitalizations were for congestive heart failure in the control group and 14 in the treatment group with the associated p-values.

Again, as the sponsor mentioned, they measured many neurohormonal levels. The statement that I would like to make about this is not that they saw a significant difference in any of the variables, but the levels that they drew were highly suggestive

of advanced heart failure.

Just a summary of the functional effectiveness endpoints. In QRS duration they did see an improvement with the treatment. In Peak $VO_2$ they saw an improvement with the treatment. IN exercise time they also saw improvement with the treatment. The echo parameters were a little variable but there was an overall improvement with the treatment. Health care utilization, no overall difference. Neurohormonal difference, there was one significant difference.

I would like to just review some of the mortality that was seen in this study during the time. There were 69 patient deaths. Six were after unsuccessful implants. Two patients were implanted but not randomized. It was clear that at least one of the deaths was related to the procedure itself.

33 percent of the deaths occurred during the six-month time. In the control group there were 19 deaths, five of which were sudden cardiac death. In the treatment group there were 14 deaths, seven of which were sudden cardiac death. Overall there was no